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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/590,492	06/01/2007	Takahide Kohro	032217A	1086

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EXAMINER	
PAGONAKIS, ANNA	

ART UNIT	PAPER NUMBER
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/590,492	KOHRO ET AL.	
	Examiner	Art Unit	
	ANNA PAGONAKIS	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *1-6; 10-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2 sheets, 8/24/2006; 6 sheets, 11/30/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election without traverse of Group II, claims 7-9, in the reply filed on 6/16/2008 is acknowledged. Claims 1-15 are pending in the application. Claims 1-6, 10-15 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected subject matter, there being no allowable generic or linking claim. Accordingly, no claims have been added, amended or cancelled.

This application is the national stage entry of PCT/JP05/03008 filed 2/24/2005.

Claims 7-9 are currently under examination and are the subject of this Office Action.

Change of Examiner

The examiner assigned to the instant application has changed. The new examiner is Anna Pagonakis. Contact information is provided at the end of this Office Action.

Information Disclosure Statement

The information disclosure statement filed on 8/24/2006 and 11/30/2006 have been received. Documents with no publication date were not considered.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7-9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In this regard, this application disclosure and claims have been compared per the factors indicated in the decision In re Wands, 8 USPQ 2d 1400 (Fed. Cir., 1988) as to undue experimentation. The factors include:

1. the nature of the invention;
2. the breadth of the claims;
3. the predictability or unpredictability of the art;
4. the amount of direction or guidance presented;
5. the presence or absence of working examples;
6. the quantity of experimentation necessary;
7. the state of the prior art; and,
8. the relative skill of those skilled in the art.

The relevant factors are addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

The instant claims are directed to a method of promoting transfer of Cdc42 protein into the nucleus by administration of fluvastatin. However, the instant specification as originally filed lacks adequate guidance, direction or discussion to apprise the skilled artisan how the claimed compound may be used to achieve the disclosed utilities for treating conditions wherein the transfer of cdc42 protein into the nucleus has been implicated. The instant specification fails to present sufficient evidence, either in the form of data or scientifically sound reasoning, which would provide a reasonable expectation that the claimed compounds would have been effective to conduct the transfer of cdc42 protein into the nucleus. Though it is noted that Applicant need not necessarily demonstrate the precise manner in which the claimed therapeutic agent(s) ameliorate a particular disease state, such a mechanism must be elucidated in cases where Applicant relies upon a correlation between the particular activity of a compound (e.g.

inhibition of a particular enzyme, binding to a particular receptor, etc.) and a reasonable expectation in efficacy in treating a particular disease.

In the instant case, Applicant provides one working example to establish that fluvastatin induces the transfer of cdc42 protein into the nucleus, with one set of cells, Example 1. Applicant provides no working examples with dosage information or administration routes and further no working examples of in vivo use in mammals and finally no representative set of working examples, including various different cell types (only one working example is provided). It is also noted that it is unclear what the Figures provided by Applicant are in fact depicting. In the absence of such, it is clear that the instant specification fails to support the enablement of the instantly claimed compounds in functioning to transfer the cdc42 protein into the nucleus.

Those of skill in the art recognize that in vitro assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. The greatly increased complexity of the in vivo environment as compared to the very narrowly defined and controlled conditions of an in vitro assay does not permit a single extrapolation of in vitro assays to human diagnostic efficacy with any reasonably degree of predictability. In vitro assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore, it is well known in the art that cultured cells, over a period of time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York., p4) teach that it is recognized in the art that there are many differences between cultured cells and counterparts in vivo. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissues are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation in vivo. Without this control, cellular metabolism may be

more constant in vitro but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4., see Differences in Vitro). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is note. Yet normal or malignant cells in vivo are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been scientific characteristics different form those in vivo and cannot duplicate the complex conditions of the in vivo environment involved in host-tumor and cell-cell interactions.

In addition, the treatment of cancer is at most unpredictable as underscored by Gura (Science, v278, 1997, pp. 1041-1042) who discusses the potential shortcomings of potential anti-cancer agents including extrapolating from in-vitro to in-vivo protocols, the problems of drug testing in knockout mice, and problems associated with clonogenic assays. Indeed since forma screening began in 1955, thousands of drugs have shown activity in either cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to supportive care, have won approval from the FDA (page 1041, column one) wherein the fundamental problem in drug discovery for cancer is that the model systems are not predictive.

As stated in MPEP 2164.04, "Doubt may arise about enablement because information is missing from one or more essential parts or relationships between parts which one skilled in the art could not develop without undue experimentation." In the instant case, the information that is missing is a clear correlation between the claimed compound and its efficacy in treating the disclosed conditions, either through specific evidence in the form of data demonstrating such a fact or at least a sound mechanistic

correlation between the claimed compound, its ability to function in such a manner and the amenability of the claimed disease state to treatment using an agent capable of functioning in this manner. Though one of skill in the art might very well know how to treat a patient with the claimed compound once a diagnosis has been made of the claimed disorder, it remains that the instant specification conspicuously fails to provide an guidance or direction in support of the reasonable expectation of success in actually leading to the transfer of cdc42 protein into the nucleus. In the absence of this information, the specification fails to provide adequate guidance and/or direction to one of skill in the art at the time of the invention that would have been enabled such a person to practice the instantly claimed invention without having to resort to undue experimentation to determine how in fact one would achieve the instantly disclosed cellular objective(s).

The basis of the present rejection is not simply that experimentation would be required, since it is clear from the state of the prior art that Applicant's disclosure and remarks that experimentation in this particular art is not at all uncommon, but that this experimentation is required in order to practice the full scope of the invention would be undue. Please reference In re Angstadt, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976), which states," The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue." Accordingly, in the absence of adequate disclosure, direction or guidance as to how one would go about using the instantly claimed compound with a reasonable expectation of successfully treating the disclosed disorder(s), it remains that the pharmaceutical, chemical and medical arts are notoriously complex such that methods of use would have been sufficiently unpredictable to warrant the need for undue experimentation to actually practice the full scope of the invention as instantly claimed.

In view of the discussion of each of the preceding seven factors, the level of skill in the art is high and is at least that of a medical doctor or scientist with several years of experience in the art.

As the cited art and discussion of the above factors establish, practicing the claimed method in the manner disclosed by Applicant would not imbue the skilled artisan with a reasonable expectation or ability to make and use the full scope of the invention as instantly claimed, given the disclosure and supporting examples provided in the present specification and the state of the art at the time of the invention. In order to actually achieve the claimed invention, it is clear form the discussion above that the skilled artisan could not rely upon Applicant's disclosure as required by 35 U.S.C. 112, first paragraph, and would have no alternative recourse but the impermissible burden of undue experimentation in order to practice the full scope of the embodiments presently claimed.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 7-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Present claim 11 is directed to a method of promoting transfer of Cdc42 protein into a nucleus.

It is unclear from the claim what the "transfer" of Cdc42 protein is from. In other words, is the transfer from the mitochondria, cytosol, cytoplasm, endoplasmic reticulum, exoplasm etc to the nucleus. Further, which if any receptors are needed to be conformationally activated in order for this transfer to take place? The skilled artisan would have been reasonably apprised of the metes and bounds of the claim limitation directed to the transfer of Cdc42 protein and would constitute infringement of the instantly claimed method.

For these reasons, the claims fail to meet the tenor and express requirements of 35 U.S.C. 112, second paragraph, and are, thus, properly rejected.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 7-9 are rejected under 35 U.S.C. 102(b) as being anticipated by Masamura et al (Arterio Thromb. Vasc. Biol, 2003, provided by Applicant).

Masamura et al. teach that HMG Co A reductase inhibitors are effective for improving arteriosclerosis and other vessel-related diseases, and one of the said statins, pitavastatin is particularly employed.

The explanation of an effect obtained when using a compound cannot confer novelty on a known process if the skilled artisan was already aware of the occurrence of the desired therapeutic effect. In other words, even if transfer of Cdc42 protein into the nucleus was not itself recognized as a pharmacological effect of administering the elected compound of Masamura et al. to a patient exhibiting artherosclerossis or other vessel-related diseases, such an effect is already known in the prior art. Though new properties of a compound are not doubt important contributions to scientific and pharmaceutical development, the assessment of patentability under 35 U.S.C. 102 is based upon the therapeutic applications and effects of the compounds, not the mechanisms or properties by which they exert such a therapeutic effect.

Please also see Ex Parte Novitski, 26 USPQ2d 1389 (Bd. Pat. App. And Inter. 1993), which stated, "The Board rejected a claim directed to a method for protecting a plant from plant pathogenic nematodes by inoculating the plant with a nematode inhibiting strain of P. cepacia. A U.S. Patent to Dart disclosed inoculating using P.cepacia type Wisconsin 526 bacteria for protecting the plant from fungal

disease. Dart was silent as to nematode inhibition but the Board concluded that nematode inhibition was an inherent property of the bacteria. The Board noted that Applicant had stated in the specification that Wisconsin 526 an 18 percent nematode inhibition rating." Analogously, in the present case, though Masamura et al does not explicitly note the function of the elected compound as a promoter of transfer of cdc42 protein into the nucleus, such a property, though only now recognized by Applicant, is an inherent property of the elected compound, absent factual evidence to the contrary.

Claims 7-9 are rejected under 35 U.S.C. 102(b) as being anticipated by Morikawa et al (Atheroscleor Thromb. Vasc. Biol, 2003, vol. 23: 512-517, provided by Applicant).

Morikawa et al. teach that HMG Co A reductase inhibitors are effective for improving arteriosclerosis and other vessel-related diseases, and one of the said statins, pitavastatin is particularly employed.

The explanation of an effect obtained when using a compound cannot confer novelty on a known process if the skilled artisan was already aware of the occurrence of the desired therapeutic effect. In other words, even if transfer of Cdc42 protein into the nucleus was not itself recognized as a pharmacological effect of administering the elected compound of Masamura et al. to a patient exhibiting artherosclerossis or other vessel-related diseases, such an effect is already known in the prior art. Though new properties of a compound are not doubt important contributions to scientific and pharmaceutical development, the assessment of patentability under 35 U.S.C. 102 is based upon the therapeutic applications and effects of the compounds, not the mechanisms or properties by which they exert such a therapeutic effect.

Please also see Ex Parte Novitski, 26 USPQ2d 1389 (Bd. Pat. App. And Inter. 1993), which stated, "The Board rejected a claim directed to a method for protecting a plant from plant pathogenic nematodes by inoculating the plant with a nematode inhibiting strain of P. cepacia. A U.S. Patent to Dart

disclosed inoculating using P.cepacia type Wisconsin 526 bacteria for protecting the plant from fungal disease. Dart was silent as to nematode inhibition but the Board concluded that nematode inhibition was an inherent property of the bacteria. The Board noted that Applicant had stated in the specification that Wisconsin 526 an 18 percent nematode inhibition rating." Analogously, in the present case, though Masamura et al does not explicitly note the function of the elected compound as a promoter of transfer of cdc42 protein into the nucleus, such a property, though only now recognized by Applicant, is an inherent property of the elected compound, absent factual evidence to the contrary.

Conclusion

No claim is found to be allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANNA PAGONAKIS whose telephone number is (571)270-3505. The examiner can normally be reached on Monday thru Thursday, 9am to 5pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

AP

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614